EIMD

European registry and network for
Intoxication type Metabolic Diseases

For healthcare professionals

Propionic Aciduria

www.e-imd.org

Disease Name, OMIM no.

Propionic acidaemia
OMIM #606054

Synonyms

Propionyl CoA carboxylase deficiency

Epidemiology

Propionic aciduria (PA) is a rare disorder and the true incidence in Europe is unknown. Estimates of incidence in Western populations have ranged from 1:50,000 to 1:500,000 births, and overall incidence is believed to be ~ 1:100-150,000. In some populations across the world, this is much higher: for example incidence in Saudi Arabia is reported to be much higher at 1 in 2000 to 5000 live births.

Etiology

- aciduriaPA is caused by the deficient activity of the enzyme propionyl CoA carboxylase, a mitochondrial biotin-dependant enzyme which is essential for the catabolism of the amino acids threonine, methionine, isoleucine, valine, as well as cholesterol and odd-chain fatty acids.
- The holoenzyme exists as a dodecamer of 2 subunits, α6β6; the α subunit harbours the biotin carboxylase (BC) and the biotin carboxyl carrier protein activity (BCCP), whilst the β subunit harbours the carboxyltransferase (CT) activity.
- The α and β subunits are respectively encoded on different genes, PCCA (locus3q21-q22) and PCCB (locus 13q32) and are synthesized separately before mitochondrial import.

- Defects in PCCA and PCCB are inherited in an autosomal recessive manner and several mutations in each gene have been described across different populations. PCCA mutations are heterogeneous and no particular mutations are found to be more prevalent than others, whereas a limited number of PCCB mutations account for a majority of alleles on Oriental and Caucasian populations. Broad genotype-phenotype correlations exist, with certain null mutations accounting for patients with a severe phenotype and certain missense mutations associated with milder phenotypes.

Clinical features

Depending on the age at presentation, patients with aciduriaPA may be classified into the early onset and late onset forms.

- Patients with **early-onset propionic (PA)** present in the first few weeks of life with acute metabolic decompensation. Classically, infants are well at birth and as feeds are introduced, they develop symptoms such as:
  - lethargy
  - poor feeding
  - tachypnea
  - vomiting
  - seizures
  - progress to coma, apnoea and death if untreated.

  The symptoms are indistinguishable for those of a sick neonate due to any cause. Investigations at presentation typically reveal metabolic acidosis with increased anion gap and hyperammonaemia; pancytopenia and hypocalcemia may also be found.

- **Late-onset** cases of PA may present later in infancy, childhood or later with a more heterogeneous clinical picture including:
  - Vomiting
  - feeding difficulties

- failure to thrive
- psychomotor retardation
- late-onset acute metabolic decompensation with acidosis, encephalopathy and hyperammonaemia
- movement disorders that may arise following decompensation or insidiously.

Natural history and long-term complications

The natural history of PA is not well characterized, although a number of complications and sequelae are well known; most of these are derived from anecdotal reports and small retrospective case series and there are no prospective studies that have described the long-term course and outcome.

- Survival: the long-term outcome of PA remains poor, particularly for the early-onset forms. Recent studies indicate long-term survival rates of ~60% in early-onset PA and >90% for late-onset PA. Most surviving individuals have varying degrees of developmental disability and neurological or other complications.

- Neurological sequelae: A number of neurological complications have been described, with or without concomitant or preceding metabolic decompensation:
    - Acute onset neurological symptoms or “metabolic strokes”
    - Basal ganglia damage to the caudate, globus pallidum and putamen
    - Extrapyramidal symptoms such as dystonia, chorea and athetosis
    - Seizures of different types, including generalized tonic-clonic, focal, myoclonic and atonic
    - Cerebral atrophy
    - Optic atrophy

- Developmental outcome: A majority of long-term survivors have gross motor, fine motor and cognitive impairment and require individualized learning plans in school.

- Cardiac complications described include:
  - Cardiac arrhythmias particularly prolonged QT interval that can predispose to ventricular ectopics, torsade de pointes, syncope and sudden death
  - Cardiomyopathy that may or may not accompany metabolic decompensation
- Skeletal muscle : Metabolic myopathy which may develop progressively in older children and adolescents as the result of secondary chronic energy impairment

- Gastrointestinal complications
  - Pancreatitis that may be recurrent and occur independently or with acute metabolic decompensation
  - Recurrent vomiting

- Other known rare complications
  - Immune dysfunction, recurrent infections and pancytopenia (particularly during acute metabolic crises)
  - An exfoliative dermatitis-like skin rash (termed “acrodermatitis acidemica”), often associated with isoleucine deficiency as a result of inadequate supply with essential nutrients and/or micronutrients
  - Decreased bone mineral density
  - Hyperglycaemia and insulin resistance

Diagnosis

- Basic metabolic tests that may lead to suspicion of PA include metabolic acidosis with increased anion gap, hyperammonaemia, lactic acidosis and hypoglycaemia.

- Specific diagnostic tests include urine organic acid analysis and plasma or blood spot acylcarnitine profiles. On urine organic acid analysis, characteristic elevations of propionic acid, propionylcarnitine, methylcitrate, 3-OH propionate are seen; additionally, other organic acids including 3-hydroxyisovalerate, tiglic acid, tiglylglycine, propionylglycine, 3-methylbutyrate and 3-hydroxy-2-methylbutyrate may also be variably detected. Plasma acylcarnitine analysis may reveal low levels of free carnitine along with elevated levels of propionylcarnitine (C3 carnitine).
- Plasma amino acid analysis may reveal hyperglycinaemia and hyperalaninaemia.
- Enzymatic confirmation of the diagnosis can be performed by demonstrating deficient propionyl CoA activity in skin fibroblasts, leucocytes and other tissues. ^{14}C propionate incorporation studies can also be used to demonstrate the enzyme defect although it does not specifically distinguish between propionic and methylmalonic acidurias.
- Mutation analysis is available for diagnostic confirmation and involves analysis of the PCCA and PCCB genes.
- Prenatal diagnosis can be undertaken in the second trimester by either direct assay of amniotic fluid for abnormal metabolites by GCMS and/or tandem MS, or in the first trimester by enzymatic assay or mutation analysis (if known) on chorionic villous samples.

Differential diagnosis

- The presenting clinical features are similar to those arising from a number of other inherited and acquired disorders, such as infections, toxicity and other inherited metabolic disorders. In an acutely sick neonate, a high index of suspicion for inherited metabolic disorders including the organic acidurias should be maintained until exclusion as the features are indistinguishable from sepsis.

- Organic acid and blood acylcarnitine profiles similar to PA can be seen in other disorders such as multiple carboxylase deficiency, biotinidase deficiency and mitochondrial disorders. Usually, other characteristic metabolites help distinguish between these conditions, but specific diagnostic tests should be carried out if the diagnosis is unclear as the treatment and prognosis of these conditions is very different to PA.

Prognosis

The long-term prognosis for PA has improved considerably in the last 2 decades, and survival rates for the severe form of >60% and >90% for the late-onset form are expected. Normal growth can be achieved with adequate dietary management. However, morbidity remains high, with a majority of patients having cognitive impairment, physical disability and neurological sequelae such as chorea, athetosis, dystonia and seizures.

Treatment

The treatment of PA is complex and requires regular monitoring and frequent therapeutic and dietary adjustments. It is recommended that the treatment and follow up of these patients be supervised by an experienced multidisciplinary team in a tertiary setting, although many aspects of care, including emergency management, can be delivered at the local or secondary level.

Patients usually require 3-monthly follow up in order to monitor their clinical condition, nutritional status and growth and to make any changes to treatment as necessary. Long-term surveillance must include annual cardiac assessments because of the potential for developing cardiac arrhythmias and cardiomyopathy in later life.

Acute management in the newborn period

- The basic principles of acute management of any neonate with a disorder of protein catabolism should be followed, including fluid and electrolyte resuscitation, correction of acid-base status, stoppage of exogenous protein, provision of sufficient calories and promotion of anabolism with insulin infusion.
- Metabolites of alternative propionate oxidation are inefficiently cleared via the kidneys and haemofiltration or haemodialysis may be necessary in order to achieve sufficient toxin removal. Peritoneal dialysis is relatively inefficient in this situation.
- Treatment of acute hyperammonaemia with carbamylglutamate (100mg/kg/day in 2-4 divided doses) in PA may help reduce ammonia levels without renal replacement therapy, and this medication should be tried if hyperammonaemia is thought to be a significant factor in causing acute encephalopathy.
- L-carnitine in a dose of 100-200mg/kg/day helps correct any carnitine depletion and facilitates removal of toxic organic acids.
- Feeds or parenteral nutrition should be commenced as soon as metabolic stabilization is achieved in order to prevent essential amino acid deficiency.
- When the infant is fit for discharge after stabilization, it is essential to educate the parents and carers about the condition and its management, including the specialized diet, medications, tube feeding and emergency management. The day-to-day management of PA is very complex and community-based services must be engaged in order to enable various aspects of care to be delivered effectively at home.

Basic (well-day treatment)

This comprises dietary treatment and pharmacotherapy.

- Dietary treatment:
  The basic principles of dietary treatment include:
  - dietary natural protein restriction to reduce the load of precursor amino acids (i.e., isoleucine, methionine, threonin, valine)
  - prevention of a catabolic state
  - provision of sufficient protein and calories to allow normal growth
  - provision of vitamin and mineral supplements to prevent deficiency states

  Individual protein tolerance varies, especially in late-onset patients and in some cases, precursor-free amino acid mixtures may be helpful in achieving adequate protein intake. Most children with PA have a very poor appetite and nasogastric or gastrostomy tube feeding is almost always required in order to maintain adequate nutritional intake. The dietary management must be supervised by a metabolic specialist dietetic team.

- Pharmacotherapy
  - L-carnitine: long-term oral/enteral carnitine in a dose of 100mg/kg/day is helpful in preventing carnitine depletion and in helping conjugate and excrete propionic acid and related toxic metabolites.
  - Metronidazole: Studies have shown that 20-30% of the body's propionic acid load is derived from microbial bacteria and suppression of gut flora has been shown to reduce urinary excretion of propionate metabolites. Metronidazole in a dose of 10-20mg/kg/day for 7-10 days every 2-3 months or alternatively given continuously in a low dose (5-7mg/kg/day) may be of significant benefit.

- Additional medications may be required to treat specific complications, e.g. dystonia, seizures, recurrent pancreatitis and cardiac arrhythmias.

Emergency management during acute illnesses

Any catabolic state, such as intercurrent infections, anaesthesia, surgery, immunization or prolonged starvation can potentially result in acute metabolic decompensation that may be life-threatening. The aim of emergency management is to prevent metabolic decompensation from occurring during these potentially catabolic situations.

The general principles of emergency management include:

- Reducing or stopping protein intake temporarily.
- Regular enteral administration of a high energy (carbohydrate or carbohydrate and lipid-based) feeds
- Normal feeds must be reintroduced within 24-48 hours
- If the emergency diet is not tolerated or there is clinical deterioration, the child must be admitted to hospital for urgent clinical and biochemical evaluation.
- In this situation, rehydration using intravenous 10% dextrose-based solutions (adapted to the age-dependant demand) usually result in clinical improvement within 24-48 hours, when regular feeds can be reintroduced. If feeds cannot be introduced in this time because of the clinical condition, a short period of parenteral nutrition may be necessary.
- Intravenous carnitine should be given in a dose of 200mg/kg/24 hours in 3 or 4 divided doses.
- Any specific biochemical disturbances (e.g. severe acidosis, hyperam-

monaemia, electrolyte disturbances) may require specific correction on advice from a tertiary metabolic unit. A high-concentration dextrose infusion with or without insulin may help promote anabolism.

- In cases of severe decompensation and worsening clinical and/or biochemical status despite the above measures, haemodialysis or haemofiltration may be necessary to enable toxin removal.

Emergency management guidelines are available via the website of the British Inherited Metabolic Disease Group website www.bimdg.org.uk

Liver transplantation

As a majority of propionyl CoA activity resides in the liver, liver transplantation can be expected to significantly improve the biochemical abnormalities. The few reported cases of liver transplantation in PA suggest improved metabolic stability; dietary relaxation may also be achieved. The experience with liver transplantation in PA, however, is limited and carries its own risks, such as increased perioperative mortality. Furthermore, as the enzyme is ubiquitously expressed, tissue-specific biochemical abnormalities persist and potentially, neurological deterioration may occur even after transplantation.

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For more information: http://ec.europa.eu/health/programme/policy/index_en.htm

For more information about e-imd: www.e-imd.org